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Attorney Docket No. PC11025A

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By Kelly A. Smith
(Signature of person mailing)
Kelly A. Smith
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

IN RE APPLICATION OF: **Charles L. Shear**

APPLICATION NO.: **09/929,862** : Examiner: **Raymond J. Henley III**

FILING DATE: **August 14, 2001** : Group Art Unit: **1614**

TITLE: **Therapeutic Combination**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

BRIEF ON APPEAL

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Appellants appeal the Final Office Action mailed June 22, 2004 which finally rejected claims 1, 4, 5 and 8-14. A Notice of Appeal was filed on November 1, 2004. A petition for a five month extension of time and fee transmittal are filed herewith.

This Brief is being filed in triplicate.

This Brief contains items identified in the Table of Contents below under the headings as required by 37 C.F.R. 1.192

TABLE OF CONTENTS

REAL PARTY IN INTEREST

This Application is assigned to Pfizer Inc., a U.S. Corporation organized under the laws of the State of Delaware and having its headquarters at 235 East 42nd Street, New York, New York USA.

RELATED INTERFERENCES AND APPEALS

The subject matter of this Appeal is not related to any co-pending Interferences or Appeals in the U.S. Patent & Trademark Office.

STATUS OF CLAIMS

1. Claims cancelled: 2, 3, 6, 7, 15-20.
2. Claims withdrawn from consideration but not cancelled: none
3. Claims pending: 1, 4, 5 and 8-14 have been rejected under 35 USC §103(a) in the final Office Action mailed June 22, 2004.
4. No claims have been allowed.

STATUS OF AMENDMENTS

All amendments have been entered without objection.

SUMMARY OF THE INVENTION

Appellant's claims are directed to a pharmaceutical composition comprising [2R, 4S]-4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (hereinafter the "CETP inhibitor compound") and certain hydroxy metabolites of atorvastatin (or their appropriate salts), in the form of a single composition (the three ingredients: the CETP inhibitor compound, atorvastatin hydroxy metabolite and a carrier, vehicle or diluent are together in a single dosage form, e.g., in the form of a tablet, capsule or suspension). Appellant discovered that the CETP inhibitor compound and atorvastatin hydroxyl metabolite, if used together in combination with a carrier, vehicle or diluent, provide a significant medical benefit.

Appellant recognizes that the two specified agents were known *per se* and, that when used alone, the agents could be administered to treat certain medical conditions. However,

what was not known, or described in the cited references, was the use of the specific agents together in a single composition.

GROUNDS OF REJECTION TO BE REVIEWED UPON APPEAL

I. Claims 1, 4, 5 and 8-14 stand rejected under 35 USC §103(a) over Deninno et al. (WO 00/17164 in view of Roth (U.S. pat. no. 4,681,893).

ARGUMENTS

I. Rejection of Claims 1, 4, 5 and 8-14 Under 35 U.S.C. §103(a).

The Examiner has rejected the claims as obvious because the difference between the references and Appellant's claimed subject matter lies in that Deninno, et al. teach only the compound atorvastatin and not the presently claimed salts and/or hydroxy acid forms thereof.

The rejection also states that to the skilled artisan, Appellant's claimed subject matter would have been obvious because Roth teaches the presently claimed salt forms and hydroxy acid forms of atorvastatin (see the abstract, column 2, line 3-43 and column 7, line 1-17) as being effective HMG-CoA reductase inhibitors. The rejection states the skilled artisan would have been motivated to alternatively use the compounds of Roth for the same purpose as the atorvastatin of Dennino et al. because Dennino et al teaches atorvastatin for its HMG-CoA reductase inhibitory activity and Roth identified his compounds as being HMG-CoA reductase inhibitors. The rejection also states that Appellant's allegation of "benefits" amounts to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references. The rejection also states that it has not been established on the record, by means of comparative experimental data, that Appellant's combination produces any results that would not have been obvious from the prior art teachings.

The rejection states that Appellant has argued that the prior art provides no motivation, teaching, suggestion or reasonable expectation of success for employing hydroxy-substituted atorvastatin with the compound taught by Deninno et al., i.e "the CETP inhibitor compound".

The rejection also states that Deninno et al. at page 29, line 26 (relied upon in the office action dated January 16, 2002 at page 3) clearly teaches that an HMG-CoA reductase inhibitor may be utilized with "the CETP inhibitor compound". The rejection also states that given this and the fact that hydroxy-substituted atorvastatin was a well known HMG-CoA reductase inhibitor, it is submitted that the art does provide motivation, teaching, suggestion and reasonable expectation of success for employing hydroxy-substituted atorvastatin with "the CETP inhibitor compound" taught by Deninno et al. thus, rendering obvious the claimed subject matter.

Appellant submits that claims 1, 4, 5 and 8-14 are not obvious over Deninno et al. in view of Roth. Appellant submits that the rejection fails to make out a *prima facie* case of obviousness.

Appellant's claims are directed to a pharmaceutical composition comprising specific drugs; hydroxy-substituted atorvastatin and "the CETP inhibitor compound", in the form of a single composition. Appellant discovered that these active chemicals, when used together in combination with a pharmaceutically acceptable carrier, vehicle or diluent, provide benefits in the treatment of certain medical conditions.

While each of these individual drugs was known *per se* and was used alone for certain medicinal purposes, such as reflected in the cited references, their specific use together in a fixed composition has not been described in the prior art cited by the Examiner for any reason whatsoever. Appellant's claims have been rejected only as obvious (35 USC §103), and the Examiner has effectively conceded the novelty of the claimed composition.

Thus, the patentability analysis begins with the fact that no one ever before combined these active ingredients into a single pharmaceutical composition. The Examiner contends, however, that the combination of the hydroxy-substituted atorvastatin and "the CETP inhibitor compound" in a single pharmaceutical composition is *prima facie* obvious.

First, applicable case law specifically addressing the combination of two agents, each known individually for the same purposes fully supports the Examiner's failure to carry the burden of establishing *prima facie* obviousness. Thus, *In re Geiger,* 2 USPQ2d 1276 (Fed. Cir. 1987) governs here. As the Federal Circuit held in *Geiger,* "at best" the combination proposed by the Examiner evidenced a general incentive to "try various combinations of these known scale and corrosion prevention agents. However, this is not the standard of 35 USC § 103." (2 USPQ2d at 1278). In *In re Geiger* the Court addressed the Board's rejection of claims to a method of inhibiting scale formation and corrosion of metal using three ingredients each of which had been separately used for this very same purpose. In reversing the Board, the Court noted (at page 1277-78):

> Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems, the board held that it would have been prima facie obvious, within the meaning of 35 UF.S.C. 103, to employ

> these components in combination for their known functions and to optimize the amount of each additive." (emphasis added).

The Appellant in Geiger contended that the "PTO has failed to establish a *prima facie* case of obviousness." *Id.* At 1278. The Federal Circuit carefully examined the prior art cited and agreed, stating:

> At best, in view of these disclosure, one skilled in the art might find it obvious to try various combinations of these known scale and corrosion prevention agents. However, this is not the standard of 35 U.S.C. 103. *Id.*

Thus, the fact that each component was broadly used in water treatment was not sufficient to establish a use "for the same purpose". Accordingly, Appellants submit that *In re Geiger* is the controlling precedent. While both the atorvastatin metabolite and "the CETP inhibitor compound" are used in the treatment of various heart conditions, their specific applications and mechanisms of action are quite different. Thus, the atorvastatin metabolite is an HMG-Co A reductase inhibitor useful for the reduction of low density lipoprotein cholesterol and the CETP inhibitor is a cholesterol ester transfer inhibitor useful for the elevation of high density lipoprotein cholesterol. Again, both compounds function through <u>different</u> mechanisms.

This is analogous to the *Geiger* Case. Even though the various scale and corrosion inhibitors at issue in *Geiger* were broadly taught to be useful in treating water, the Federal Circuit held that insufficient to sustain a finding of *prima facie* obviousness.

Appellant also submits that there is <u>no teaching or suggestion</u> in the art that these particular drugs should be selected from the vast array of available compounds and combined in a single pharmaceutical composition. At best, the art supports only an "obvious to try" situation (which Appellant does not concede).

In presenting this argument regarding "obvious to try," Appellant submits that for *prima facie* obviousness to exist (see MPEP §2142) for the combination of hydroxy-substituted atorvastatin and "the CETP inhibitor compound" in a single pharmaceutical composition, there must be a <u>motivation</u> for making such a composition. Some reason must exist <u>from the teachings of the references</u> (and not via hindsight) to <u>select</u> these specified ingredients and put them together in a single pharmaceutical composition. Specifically, Deninno et al. recites a

whole host of specific CETP inhibitors and embraces a genus of an even greater number of CETP inhibitors. In addition, Roth teaches a vast amount of HMG-Co A reductase inhibitors in additon to the hydroxy metabolites of atorvastatin. Appellants submit that there is simply no direction to select these two specific compounds out of all the possible combinations of HMG-Co reductase inhibitors (Roth) and CETP inhibitors (Deninno). There are many classes of cardiovascular agents, and a far greater number of individual agents withinin each of those classes. Nothing but hindsight allows one to pluck these two specific agents from the many known in order to reconstruct the instant claims. In analogous genus-species cases the Federal Circuit has decided against *prima* facie obviousness, *In re Baird,* 16 F.3d 380, (Fed. Cir. 1994); *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992).

It is not enough simply to say that there is a general teaching or desire to combine materials -- instead, one skilled in the art must be motivated by some teaching in the art to make the specific combination claimed. And, assuming such motivation (which Appellant submits does not exist here) the Examiner has the initial burden to establish both motivation and reasonable expectation. Restated, the law is clear that the Examiner must first establish, from the art, the motivation to select the ingredients and establish a reasonable expectation of success. If the rejection does not provide both, Appellant is under no obligation to rebut any presumption, e.g., by providing evidence of an unexpected result. MPEP §2142.

In short, the cited references simply do not establish *prima facie* obviousness under the legal requirements of 35 U.S.C. §103 as established by MPEP, the applicable statute and the decided case law. Consequently, Appellant respectfully requests that the obviousness rejection be withdrawn, and this application be passed to issue.

The Federal Circuit's admonition that combinations of old elements (*i.e.*, elements *per se* taught in the art even for the same purpose as claimed) can still be patentable was restated in *The Gillette Company v. S.C. Johnson & Son, Inc.,* 15 U.S.P.Q.2d 1923 (Fed. Cir. 1990):

> It is true that [the claimed invention] consists of a combination of old elements so arranged as to perform certain related functions. It is immaterial to the issue, however, that all of the elements were old in other contexts. *What must be found obvious to defeat the patent is the claimed combination.*

And the Court carefully distinguished the legal standard of obviousness from "obvious to try":

> [a]n "obvious-to-try" situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued. *** However, we have consistently held that "obvious to try" is not to be equated with obviousness under 35 USC 103.

See also In re Fine, 5 U.S.P.Q.2d 1596, 1598-9 (Fed. Cir. 1988) (no *prima facie* obviousness; "obvious to try" is "not a legitimate test of patentability"); *In re Jones*, 21 U.S.P.Q. 1941 (Fed. Cir. 1992) (no *prima facie* obviousness even though the prior art generically taught Applicants' claimed substituted amine salt of dicamba and the specific salt moiety was known for other acids); *Ecolochem, Inc. v. Southern California Edison Co.*, 56 U.S.P.Q.2d 1065, 1072-3 (Fed. Cir. 2000); *In re Antonie,* 195 U.S.P.Q. 6, 8 (CCPA 1977) and *In re Tomlison*, 150 U.S.P.Q. 623, 626 (CCPA 1966).

Applicant also respectfully refers the Examiner to the MPEP, Section 2142, where the legal concept of *prima facie* obviousness is explained in detail with applicable illustrations and cited authority. As stated there:

1. The concept of *prima facie* obviousness is a "procedural tool of examination" which "allocates who has the burden of going forward with production of evidence in each step of the examination process";
2. The Examiner "bears the initial burden of factually supporting any *prima facie* conclusion of obviousness";
3. If the Examiner "does not produce a *prima facie* case, the Applicant is under no obligation to submit evidence of nonobviousness"; and
4. In determining whether a *prima facie* case of obviousness exists, the Examiner is cautioned "that impermissible hindsight must be avoided and the legal conclusion [of *prima facie* obviousness] must be reached on the basis of the facts gleaned from the prior art".

MPEP §2142 further advises as follows regarding what is required before the Examiner can establish *prima facie* obviousness:

> "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure."

See also MPEP §§2143 et seq and the legal authorities and factual examples there set forth.

With these admonitions from the Federal Circuit, the MPEP and its cited supporting case law in mind, Appellant submits that the threshold issue becomes whether the Examiner has carried the burden to establish *prima facie* obviousness from the cited references -- is there something in the art that motivates a skilled worker to combine the claimed specific materials into a single pharmaceutical composition coupled with a reasonable expectation that if this were done, a beneficial result would be obtained?

Appellant respectfully submits that the answer is "no", and therefore no case of *prima facie* obviousness has been established. Thus, this application should be passed to issue.

Further, the motivation to modify the prior art must flow from some teaching in the art that suggests the desirability or incentive to make the modification needed to arrive at the claimed invention. "The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification." *In re Laskowski*, 10 U.S.P.Q.2d 1397, 1399 (Fed. Cir. 1989).

Again, the rejection does not detail reasoning that provides the motivation to modify the prior art atorvastatin to attain the hydroxyl metabolite of atorvastatin and then to combine the compound so modified with "the CETP inhibitor compound" and thus the rejection does not present a *prima facie* case of obviousness.

It is Appellant's position that "obvious to try" is not the standard for patentability, and that the Examiner did not make out a *prima facie* case because, *inter alia* (1) the references provide no effective motivation or suggestion that the administration of the specific

combination could or would be useful for the treatment of atherosclerosis. The law is emphatic that "obvious to try" is not the standard for patentability.

"Obvious to try" is NOT the test of obviousness under 35 U.S.C. §103. *American Hospital Supply Corp. v. Travenol Laboratories, Inc.*, 223 USPQ 577, 582 (Fed. cir. 1984). The Federal Circuit has explained the proper test:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out **and would have a reasonable likelihood of success**, viewed in light of the prior art. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** (emphasis added).

In re Dow Chemical Co., 5 USPQ.2d 1529, 1531 (Fed. Clir. 1988); *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.* 18 USPQ.2d 1016. 1022-23 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

The art cited by the Examiner, at most, makes it no more than perhaps obvious to explore the area of combinations generally, and this is one of the classic hallmarks of an "obvious to try" rejection:

> "The admonition that 'obvious to try' is not the standard under §103 has been directed mainly at two kinds of error. In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful...**In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.**"

In re O'Farrell, 7 USPQ2d 1673, at 1681, (Fed. Cir. 1988), emphasis supplied.

It is further noted that "[t]he issue of obviousness is determined entirely with reference to a hypothetical person having ordinary skill in the art. It is only that hypothetical person who is presumed to be aware of all the prior art. The actual inventor's skill is irrelevant to the

inquiry, and this is for a very important reason. The statutory emphasis is on a person of ordinary skill. Inventors, as a class, according to the concepts underlying the Constitution and the statutes that have created the patent system, possess something -- call it what you will -- which sets them apart from the workers of ordinary skill, and one should not go about determining obviousness under section 103 by inquiring into what patentees (i.e. inventors) would have known or would likely have done, faced with the revelations of references. A person of ordinary skill in the art is also presumed to be one who thinks along the line of conventional wisdom in the art and is not one to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights, it makes no difference which." *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985).

Thus, even if an argument could be made that the art provides a suggestion to explore the use of such combinations generally to treat atherosclerosis, this amounts, perhaps, to inviting experimentation, i.e., to perhaps making testing such compounds obvious to try, which again is manifestly not the standard for patentability. *O'Farrell*, supra.

CONCLUSION

For the foregoing reasons Appellant requests that the rejections of claims 1, 4, 5 and 8-14 under 35 U.S.C. §103(a) be reversed.

Respectfully Submitted By:

6/1/05
Date

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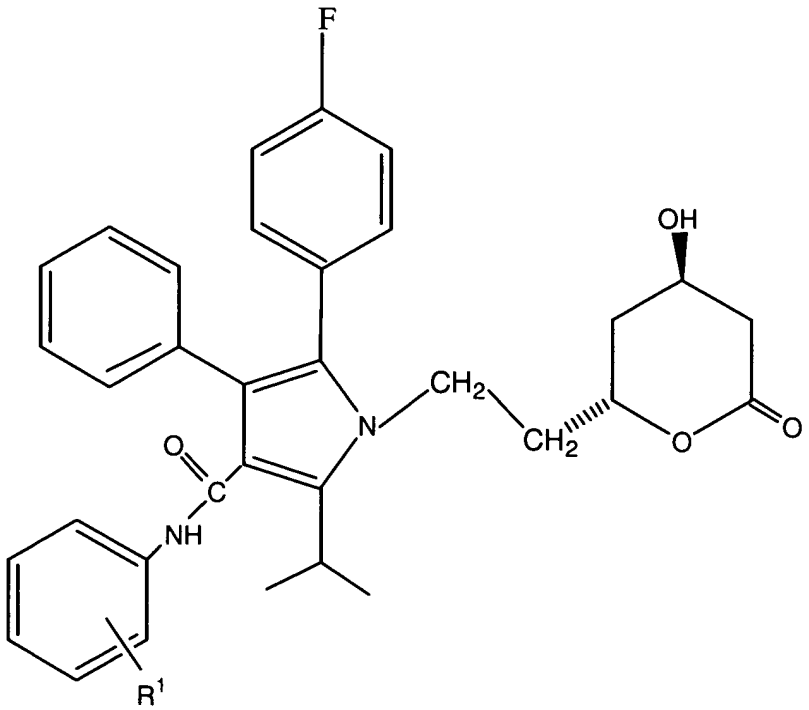
APPENDIX A

CLAIMS ON APPEAL

1. (Previously Presented) A pharmaceutical composition comprising a therapeutically effective amount of a composition comprising:

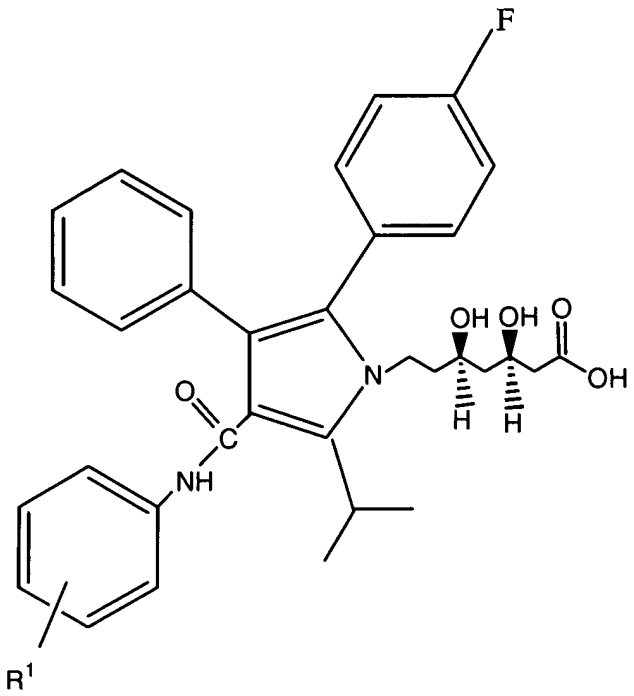
a. [2R, 4S]4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester;

b. a compound of the Formula I



Formula I

or, the open chain Formula IA



Formula IA

wherein R^1 is hydroxy or the pharmaceutically acceptable salts thereof; and

c. a pharmaceutically acceptable carrier, vehicle or diluent.

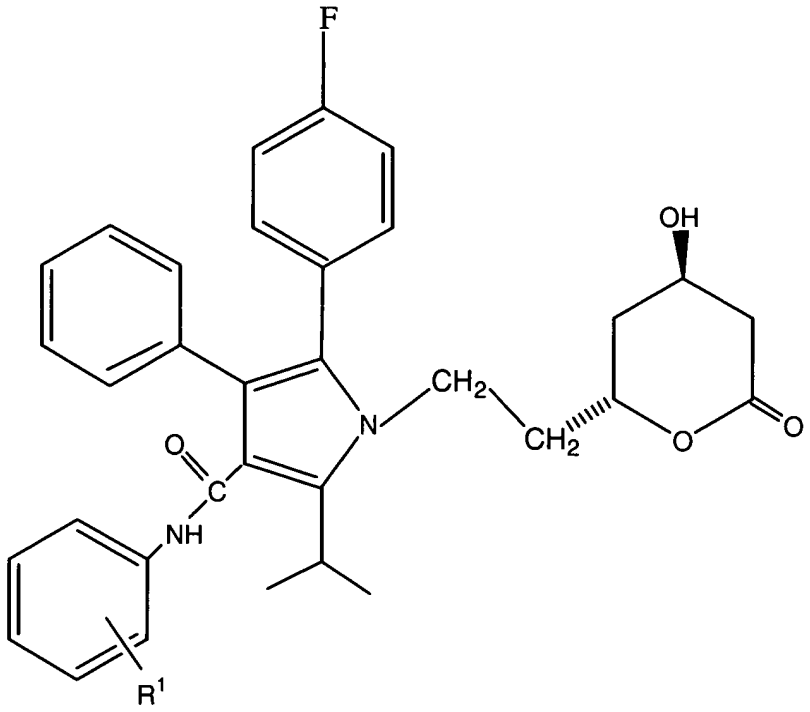
2. - 3. (Cancelled)

4. (Original) A pharmaceutical composition as recited in claim 1 wherein R^1 is 2-hydroxy or a pharmaceutically acceptable salt thereof.

5. (Previously Presented) A method for slowing the progression of atherosclerotic plaques, causing the regression of atherosclerotic plaques or managing cardiac risk, or treating atherosclerosis, hyperlipidemia, HDL elevation or angina in a mammal in need of therapeutic treatment comprising administering to said mammal a therapeutically effective amount of:

a. a first compound, said first compound being [2R, 4S]4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester; and

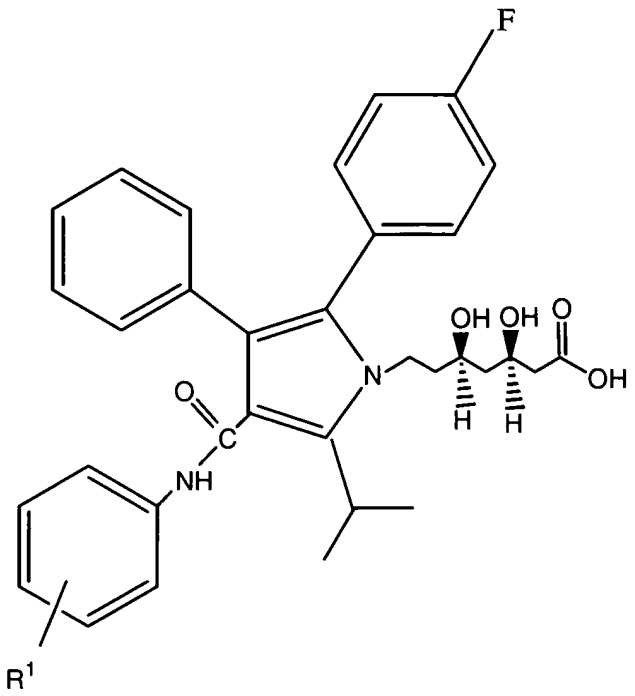
b. a second compound, said second compound being a compound having the



Formula I

Formula I

or, the open chain Formula IA



Formula IA

wherein R^1 is hydroxy or the pharmaceutically acceptable salts thereof; and wherein said first compound and said second compound are each optionally and independently administered together with a pharmaceutically acceptable carrier, vehicle or diluent.

6. - 7. (Cancelled)

8. (Original) A method of treating a mammal as recited in claim 5 wherein R^1 is 2-hydroxy or a pharmaceutically acceptable salt thereof.

9. (Original) A method of treating a mammal as recited in claim 5 wherein atherosclerosis is prevented or treated.

10. (Original) A method of treating a mammal as recited in claim 5 wherein the progression of atherosclerotic plaques is slowed.

11. (Original) A method of treating a mammal as recited in claim 10 wherein the treatment of atherosclerosis causes the regression of atherosclerotic plaques.

12. (Original) A method of treating a mammal as recited in claim 5 wherein the therapeutic treatment comprises HDL elevation treatment and antihyperlipidemic treatment.

13. (Original) A method of treating a mammal as recited in claim 5 wherein angina is prevented.

14. (Original) A method of treating a mammal as recited in claim 5 wherein the therapeutic treatment comprises cardiac risk management.

15. - 20. (Cancelled)

APPENDIX B

LITERATURE CITED

COPIES OF CITED REFERENCES PROVIDED HEREWITH

Deninno et al. (WO 00/17164)

Roth (U.S. pat. no. 4,681,893)